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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,125	02/21/2006	Andrew Chee-Yuen Chan	11669.0150USW2	2225

23552 7590 06/06/2007
MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
06/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,125	CHAN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment has been entered. Claims 1-17 are pending and under current examination.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/434,115 or 60/476,481, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. These provisional applications are directed to CD20 antibodies, no transgenic animal was disclosed. Accordingly, the priority date for instantly claimed subject matter has been established as the filing date of the PCT application, i.e. 12/11/2003.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by *Reisner et al* (USP 5,849,288).

Claim 9 is directed to an agent capable of treating a B cell lymphoma, and Claim 12 is directed to an agent capable of depleting cells expressing human CD20. The specification teaches that administration of an anti-CD20 antibody to an animal would lead to depletion of B cells (e.g. Specification, fig. 13), which would also kill B lymphoma cells, and thus treating B cell lymphoma.

Reisner et al disclose an anti-CD20 antibody capable of recognizing human B-lymphocytes expressing CD20 on the surface (e.g. figure 6). Accordingly, *Reisner et al* anticipate instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

These claims are directed to a genus of agents capable of depleting or killing cells expressing human CD20. However, other than the anti-CD20 antibody, the specification fails to reduce to practice, or provide distinguishing identifying characteristics as evidenced by other descriptions with respect to the chemical structures of the genus of agents. Accordingly, the specification fails to provide an adequate written description for what is now claimed.

In analyzing whether the written description requirement is met for the claimed subject matter i.e. a genus of agents, a representative number of species is need by their chemical structures and other relevant identifying characteristics. However, the only disclosed species in the specification is an anti-CD20 antibody. Considering the numbers and variety of agents that may be embraced by the genus, the one exemplary embodiment is not the representative species of the genus.

An adequate written description for an agent requires more than a mere statement that it is part of the invention; what is required is a description of the structure of the agent itself. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The Revised Interim Guidelines state, "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION *OF THE INVENTION*. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED.*" (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of or representative species of agents capable of depleting cells expressing human CD20. Therefore, only the described anti-CD20 antibody meets the written description provision of 35 U.S.C. §112, first paragraph.

To the extent that the claimed agents are not adequately described in the instant disclosure, claims 9 and 12 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described, which is not conventional in the art.

Claims 1-8, 10, 11, 13, 14, 16, 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a transgenic mouse whose genome comprises a homozygous insertion of a nucleic acid encoding human CD20, does not reasonably provide enablement for making and using a transgenic *animal* beyond the mouse whose genome comprises a homozygous insertion of a nucleic acid encoding human CD20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims broadly encompass any transgenic animal whose genome comprises a nucleotide encoding human CD20. Although the specification teaches generating transgenic mice whose genome comprises a polynucleotide encoding a human CD20, the specification fails to provide guidance for generating any other transgenic non-

human animals. For example, the specification provides a working example, making a transgenic mouse expressing human CD20 by microinjection, wherein the human CD20 coding sequence randomly inserted into the genome of mouse. But the specification fails to provide any relevant teachings or guidance with regard to the production of a transgenic animal as claimed by microinjection, and one of skill would not be able to rely on the state of the transgenic art for an attempt to produce transgenic non-human animals for the breadth claimed. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms, which prevent expression of the transgene, such as DNA methylation or deletion from the genome (*Kappell et al*, Current Opinion in Biotechnology 1992;3:548-53, page 549, col. 2, parag. 2). *Mullins et al* (1993) states that not all animals express a transgene sufficiently to provide a desired phenotype as the integration of a transgene into difference species of animal has been reported to give divergent phenotypes (*Mullins et al* 1993, Hypertension 22:630-3, page 631, col. 1, parag. 1, lines 14-17). *Hammer et al* (J Anim Sci 1986;63:269-78) report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (*Houdebine*,

J. Biotech. 1994;34:269-87, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (*Wall* 1996, Theriogenology 45,57-68, page 61, parag. 2, line 9 to page 62, line 3). *Wall et al* (J Dairy Sci 1997;80:2213-24) further report that "TRANSGENE EXPRESSION AND THE PHYSIOLOGICAL CONSEQUENCES OF TRANSGENE PRODUCTS IN LIVESTOCK ARE NOT ALWAYS PREDICTED IN TRANSGENIC MOUSE STUDIES" (page 2215, first paragraph). *Mullins et al* disclose that "THE USE OF NONMURINE SPECIES FOR TRANSGENESIS WILL CONTINUE TO REFLECT THE SUITABILITY OF A PARTICULAR SPECIES FOR THE SPECIFIC QUESTIONS BEING ADDRESSED, BEARING IN MIND THAT A GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER." (*Mullins et al*, J. Clin. Invest. 1996 ;98 :S37-40, page S39, Summary). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (*Cameron*, Molec. Biol. 1997;7:253-65, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (*Cameron* 1997, Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (*Cameron* 1997, Molec. Biol. 7, page 256, lines 10-13). Further, *Sigmund* (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (*Sigmund*, Arteroscler. Throm. Vasc. Biol. 2000;20:1425-9, page 1426, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, *Niemann* (1998) states that transgenic pigs

made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (*Niemann*, Transg. Res. 1998;7:73-5, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). *Wilmut* (Cloning Stem Cell 2003;5:99-100) teaches, "BY THE TIME OF DOLLY'S DEATH IN 2003, CLONES HAD BEEN DERIVED FROM ADULT CELLS OF SEVERN MAMMALIAN SPECIES, BUT THE SAME TECHNIQUES WERE NOT SUCCESSFUL IN SEVEN OTHERS, DESPITE INTENSIVE EFFORTS BY EXPERIENCED RESEARCH TEAMS. THESE INCLUDE RHESUS MONKEY, RAT, DOG, AND HORSE. THIS FAILURE EMPHASIZES THE IMPORTANCE OF DIFFERENTCES BETWEEN SPECIES. THE DIFFERENCE MIGHT BE IN THE MOLECULAR MECHANISMS THAT REGULATE EARLY DEVELOPMENT OR IN ENABLING TECHNIQUES FOR OOCYTE RECOVERY, EMBRYO CULTURE, OR EMBRYO TRANSFER. SUCH DIFFERENCES HAVE ALREADY BEEN IDENTIFIED BETWEEN THE SPECIES FROM WHICH CLONES HAVE BEEN DERIVED" (emphasis added).

While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human animal whose genome comprises a human CD20, other than the exemplified transgenic mouse, it would have required undue experimentation to predict the results achieved in any one host laboratory animal comprising and expressing a hCD20, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. Since the specification fails to disclose representative species of transgenic animals encompassed by the claims there is no way to predict the outcome of the claimed invention. Accordingly, it is concluded that the

specification fails to provide an enabling disclosure to support the full scope of the claimed invention.

As to the method claims, since the essential materials, i.e. the genus of the non-human transgenic animals are not readily available to the public, it would required undue experimentation for those intending to practice the invention.

Claim 10 is drawn to a method of identifying an agent capable of depleting cells expressing human CD20, which encompasses any type of cells, wherein the method steps are performed on B lymphocytes. The specification fails to teach how the test on B lymphocytes are related to any and all cell types, and thus fails to provide an enabling disclosure for what is now claimed.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-12, 16, 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation "the level of B lymphocytes". It is unclear what the term "level" encompasses, and thus the metes and bounds of the claims are uncertain. Further, the recitations in steps a & b are

inconsistent with step c, because the number of B-lymphocytes is the identifying criteria in step c, whereas the level is to be measured in steps a & b.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
May 29, 2007